

Amendments to the Claims

The listing of claims will replace all prior versions, and listings of claims in the application.

1. (currently amended) A method for producing a biomolecule of interest in a host cell that is not secreted by the host cell, comprising the steps of
 - a) cultivating host cells to produce the biomolecule of interest and optionally harvesting and resuspending the cells to form a cell suspension,
 - b) disintegrating the cells by alkaline lysis by contacting the cell suspension with an alkaline lysis solution and allowing the cell suspension and the alkaline lysis solution to flow through a lysis reactor that is filled with particulate material, thereby forming a lysed cell solution,
 - c) precipitating the cell debris and impurities by neutralizing the ~~lysate~~ lysed cell solution in a neutralization reactor to form a mixture comprising a precipitate and a lysate,
 - d) separating the lysate from the precipitate ~~obtained in step c)~~ wherein the mixture comprising the precipitate and the lysate is allowed to flow downward through a clarification reactor that is partially filled with retention material to form a retention layer, whereby the precipitate is retained on top of and within the retention layer and the cleared lysate leaves the reactor through the bottom of the reactor, and
 - e) purifying the biomolecule of interest,
wherein the lysis reactor is directly connected to the neutralization reactor, and wherein the neutralization reactor is directly connected to the clarification reactor

~~wherein in step d) the mixture comprising the precipitate and the lysate is allowed to gently flow downward through a clarification reactor that is partially filled, in its lower part, with retention material to form a retention layer, whereby the precipitate is retained on top of and within the retention layer of retention material and the cleared lysate leaves the reactor through the bottom of the reactor.~~

2. (currently amended) The method of claim 1, wherein the lysate ~~of step d)~~ contains the biomolecule of interest.

3. (currently amended) The method of claim 1, wherein the retention layer ~~in the reactor of step d)~~ is composed of a particulate material.

4. (original) The method of claim 3, wherein the retention layer consists of glass beads.

5. (currently amended) The method of claim 1, wherein the retention layer ~~in the reactor of step d)~~ is composed of rigid retention material.

6. (original) The method of claim 5, wherein the retention material comprises sinter plates.

7. (currently amended) The method of claim 1, wherein in step d), increasing pressure is applied to the mixture from the top of the clarification reactor, thereby ~~accelerating the process and~~ ensuring a constant outflow of the lysate.

8. (currently amended) The method of claim 7, wherein pressure is increased by ~~applying~~ applying pressurized air.

9. (original) The method of claim 1, wherein one or more wash steps are inserted between steps d) and e).

10. (canceled)

11. (currently amended) The method of claim 1 ~~10~~, wherein the flow of the cell suspension and the flow of the alkaline lysis solution are combined, without further mixing, before entering the lysis reactor, thus forming a single flow that is thoroughly ~~and gently~~ mixed when flowing through the particulate material in the lysis reactor.

12. (currently amended) The method of claim 1 ~~10~~, wherein the cell suspension and the lysis solution are introduced into the lysis reactor in the form of two independent flows.

13. (original) The method of claim 12, wherein said two flows are introduced through inlets that are situated close to each other.

14. (currently amended) The method of claim ~~11 or 12~~ or 13, wherein said two flows are transported at a defined ratio of flow rates, thereby ensuring a constant ratio of cell suspension and lysis solution volumes.

15. (currently amended) The method of claim 1, wherein in step c), the lysed cell solution obtained in step b) is mixed with a ~~the~~ neutralizing solution in a continuous mode.

16. (currently amended) The method of claim 15, wherein the lysed cell solution and the neutralizing solution are combined at a constant ratio of flow rates, ~~thereby ensuring mixing, neutralizing and precipitating during transportation between step b) and step d).~~

17. (original) The method of claim 1, wherein a concentration and/or a conditioning step is inserted between step d) and step e).

18. (currently amended) The method of claim 17, wherein a concentration step and a condition step are inserted, and wherein said concentration step takes place before said conditioning step.

19. (original) The method of claim 1, wherein said biomolecule of interest is a polynucleotide.

20. (currently amended) The method of claim 19 ~~17~~, wherein the polynucleotide is plasmid DNA.

21. (canceled)

22. (canceled)

23. (currently amended) The method of claim 1 ~~21 or 22~~ wherein, in addition, step a) is operated in a continuous mode ~~by being connected to step b)~~.

24. (currently amended) The method of claim 1, wherein the host cells ~~cell~~ mass obtained in step a) are ~~is~~ cryo-pelleted.

25. – 39. (canceled)